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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,612	02/26/2002	Marco Guida	4389-5-C1	8119

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GENAISSANCE PHARMACEUTICALS
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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,612	GUIDA ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) ~~Paper No(s)~~ * .
* filed 4/24/02; 4/26/02; 9/11/02
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Notice to Comply

DETAILED ACTION

Priority

1. It is noted that the instant application is a continuation-in-part of application no. 09/144,367, filed August 31, 1998, now U.S. Patent No. 6,432,639. While Applicants' specification does include a specific reference to this application (as well as to provisional application no. 60/271,630), the current status of the '367 application is not provided. Accordingly, the first line of the specification should be amended so as to indicate that the '367 application is "now Patent No. 6,432,639."

2. It is noted that neither application no. 09/144,367 nor provisional application no. 60/271,630 provide basis for the claimed invention. For example, neither the '367 application nor the '630 application disclose the CYP3A5 or GSTM1 mutations recited in the instant claims. Further, neither the '367 application nor the '630 application provide evidence that any of the recited polymorphisms are associated with reduced substrate metabolism. Accordingly, the effective filing date of the instant claims is the filing date of the instant application, i.e., **February 26, 2002** (see *Hunt Co. v Mallinckrodt Chemical Works*, 177 F.2d 583,587, 83 USPQ 277, 281; MPEP 201.11).

Election/Restriction

3. Applicant's election without traverse of Group III, claims 17-34, in the Amendment and Response filed July 7, 2003 is acknowledged. It is noted that non-elected claims 1-16 were canceled by that Amendment, and that claims 17-34 are now pending and under consideration.

Information Disclosure Statement

4. Regarding the information disclosure statement filed April 26, 2002, it is noted that the examiner has corrected the citation for document BG.

Compliance with Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821-25 for the reasons set forth on the attached Notice to Comply with Requirements For Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures. Applicants must comply with the requirements of 37 CFR 1.821-25 in response to this Office action. In particular, Applicant is required to submit a CRF and paper copy of the Sequence Listing containing all disclosed sequences (see, for example, the sequences at pages 26-29, 31, and 34, which were not included in the original Sequence Listing), an amendment directing the entry of the Sequence Listing into the specification, (if necessary) an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification, and a letter stating that the content of the paper and computer readable copies are the same.

Specification

6. The use of the trademark s GENEAMP, MICROCON, TAQMAN, and AMPLITAQ have been noted in this application. The trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

7. The title of the invention is not descriptive of the elected invention, which is drawn to methods only. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Methods for evaluating the ability to metabolize pharmaceuticals.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 25-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for selecting cancer treatments in which cyclophosphamide (Cy) and BCNU are not selected for administration when the CYP3A4 and CYP3A5 polymorphisms of the claims are present, and in which Cy and BCNU are selected when the CYP3A4 and CYP3A5 polymorphisms of the claims are absent, does not reasonably provide enablement for methods in which Cy and BCNU are not selected when the GSTM1 null mutation is present (see claims 25-29), or for methods in which Cy and BCNU are selected when the GSTM1 null mutation is absent (see claims 30-34). The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

It is unpredictable as to whether one of skill in the art could use applicants' invention in a manner reasonably commensurate with the claims. In keeping with the recitations of claims 25-34 regarding CYP3A4 and CYP3A5, the teachings of the specification do establish that the CYP3A4 and CYP3A5 mutations encompassed by the claims are associated with increased Cy and BCNU blood concentrations and decreased median survival in patients having these mutations who are treated with these agents (see examples 2-3). However, the specification also discloses that the GSTM1 null mutation correlates with low blood concentrations of BCNU and improved patient survival (see example 4). Accordingly, while the claims require that BCNU treatment not be selected when the GSTM1 null mutation present (and that it be selected when the null mutation is absent), the teachings of the specification, by

suggesting that those with the GSTM1 null mutation are more likely to benefit from BCNU than those without it, would lead one of skill in the art to conclude that treatments opposite to those required in the claims should be selected (i.e., that BCNU treatment should be selected when the mutation is present, and not be selected when the mutation is absent). For example, the specification states at page 36 that applicant's data "suggest that absence of the GSTM1 genes may be beneficial in effective treatment with BCNU." Thus, the specification does not provide evidence that would lead one to select BCNU for the treatment of patients lacking the GSTM1 null mutation. Further, the specification provides no evidence with respect to whether the GSTM1 null mutation is or is not associated with Cy response. Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance and enablement of a claimed invention. However, in the instant case, the prior art as exemplified by Petros et al (Proceedings of the American Association for Cancer Research Annual Meeting 42:266 [3/2001]) affirms applicants' findings that those having the GSTM1 null mutation are more likely to benefit from BCNU (see entire abstract), while the prior art as exemplified by Ambrosone et al (Cancer Research 61:7130-7135 [10/2001]) teaches that patients possessing the GSTM1 null mutation are more likely (not less likely) to benefit from Cy treatment (see entire reference, particularly pages 7131-7132). Accordingly, as both the teachings of the specification and of the art contradict claims 25-34 as written with regard to the selection of treatment for patients with the GSTM1 null mutation, it would require undue experimentation to use applicants' invention as claimed. While one of skill in the art could clearly practice

methods for selecting cancer treatments in which cyclophosphamide (Cy) and BCNU are not selected for administration when the CYP3A4 and CYP3A5 polymorphisms of the claims are present, and in which Cy and BCNU are selected when the CYP3A4 and CYP3A5 polymorphisms of the claims are absent, the specification and the prior art do not reasonably provide enablement for methods in which Cy and BCNU are not selected when the GSTM1 null mutation is present (see claims 25-30), or for methods in which Cy and BCNU are selected when the GSTM1 null mutation is absent (see claims 30-34).

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 17-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17-24 are indefinite over the recitation of the language "detecting the presence or absence in said individual of a polymorphism..." in claim 17, step (b). First, as this method step refers back to "said individual" but not to, e.g., the sample of step (a), it is unclear as to how these two steps relate to one another (i.e., is step (b) intended to require the use of the sample of step (a)?). Second, it is unclear as to how the step of detecting "polymorphism" relates back to the claim objective of detecting "a variant gene," as step (b) does not make reference to detection of a variant gene. Clarification is required.

Claim 18 is indefinite over the recitation of the limitation "said nucleic acid sequences" because there is insufficient antecedent basis for this limitation in the claims.

Claim 19 is indefinite because it is unclear as to how the recitation "wherein the step of detecting is selected from the group consisting of a cDNA assay and a genomic DNA assay" limits claim 17. The claim as written appears to broaden (rather than narrow) claim 17, by requiring only any type of "cDNA assay" or any type of "genomic DNA assay." Accordingly, the claim should be amended so as to make clear how claim 19 further limits the "detecting" of step (b) in claim 17.

Claim 20 is indefinite over the recitation of the limitations "the step of digesting," "said nucleic acid sequence," and "the corresponding wildtype sequence" because there is insufficient antecedent basis for these limitations in the claims.

Claim 21 is indefinite over the recitation of the limitation "the nucleic acid molecule of the individual" because there is insufficient antecedent basis for this limitation in the claims.

Claims 25-29 are indefinite over the recitation of the limitation "said individual" in claim 25 because there is insufficient antecedent basis for this limitation in the claims, and further because it is unclear as to how this "individual" relates to the "patient" of the claim preamble.

Claims 25-29 are indefinite over the recitation of the limitation "detecting the presence or absence in said individual of a polymorphism" in claim 25. As this method step refers back to "said individual" but not to, e.g., the sample of the prior method step,

it is unclear as to how these two steps relate to one another (i.e., is the "detecting" step intended to require the use of the sample of the "obtaining" step?).

Claims 25-29 are indefinite over the recitation of the phrase "selecting....if one or more of said polymorphisms are present" in claim 25. It is noted that the prior method steps of the claim require "obtaining" a sample comprising a single isolated gene and "detecting" a single polymorphism. It is unclear as to whether the claims are intended to be drawn to methods in which a single polymorphism is detected and employed in "selecting," or to methods encompassing detection of, e.g., one or more polymorphisms in one or more of the recited genes. Clarification is required.

Claim 27 is indefinite because it is unclear as to how the recitation "wherein the step of detecting is selected from the group consisting of a cDNA assay and a genomic DNA assay" limits claim 25. The claim as written appears to broaden (rather than narrow) claim 25, by requiring only any type of "cDNA assay" or any type of "genomic DNA assay." Accordingly, the claim should be amended so as to make clear how claim 27 further limits the "detecting" step of claim 25.

Claim 28 is indefinite over the recitation of the limitations "the step of digesting," "said nucleic acid sequence," and "the corresponding wildtype sequence" because there is insufficient antecedent basis for these limitations in the claims.

Claim 29 is indefinite over the recitation of the limitation "the nucleic acid molecule of the individual" because there is insufficient antecedent basis for this limitation in the claims.

Claims 30-34 are indefinite over the recitation of the limitation "said individual" in step (b) of claim 30, and because it is unclear as to how steps (a) and (b) relate to one another and to "selecting a treatment." First, there is insufficient antecedent basis for the limitation "said individual." Second, it is noted that step (a) encompasses "obtaining a nucleic acid sample" without any restriction as to the origin of the sample (i.e., the claim does not require obtaining a sample from a patient or from an individual), while step (b) requires detecting polymorphisms in "said individual." It is unclear as to how steps (a) and (b) relate to one another (e.g., is the "detecting" step intended to require the use of the sample of the "obtaining" step?), and as to how the "individual" of step (b) relates to the "patient" of the claim preamble.

Claim 31 is indefinite because it is unclear as to how the claim further limits claim 30, from which it depends. It is noted that claim 30 includes a step of "selecting a cancer treatment" only "if none of said polymorphisms are present." Accordingly, it is unclear as to how performing further method steps on an individual "having one of said polymorphisms" relates to the method of claim 30, which is drawn to "selecting a treatment for a cancer patient."

Claim 32 is indefinite because it is unclear as to how the recitation "wherein the step of detecting is selected from the group consisting of a cDNA assay and a genomic DNA assay" limits claim 30. The claim as written appears to broaden (rather than narrow) claim 30, by requiring only any type of "cDNA assay" or any type of "genomic DNA assay." Accordingly, the claim should be amended so as to make clear how claim 32 further limits the "detecting" step of claim 30.

Claim 33 is indefinite over the recitation of the limitations "the step of digesting," "said nucleic acid sequence," and "the corresponding wildtype sequence" because there is insufficient antecedent basis for these limitations in the claims.

Claim 34 is indefinite over the recitation of the limitation "the nucleic acid molecule of the individual" because there is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 17-19, 21, and 24 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Rebbeck et al (U.S. 6,174,684 [1/2001]).

It is first noted that the specification discloses at, e.g., page 13, that the CYP3A4 A to G polymorphism disclosed in the specification may be described as being at position –392 of CYP3A4 relative to the CYP3A4 start codon, or at position –290 of CYP3A4 with respect to the CYP3A4 transcription initiation site.

Rebbeck et al disclose and exemplify obtaining DNA samples including the cyp3A4 gene from cancer patients, and detecting the presence or absence in said samples of the cyp3A4 A to G polymorphism located at position –392 relative to the cyp3A4 start codon (see entire reference, particularly col 3, lines 10-65; Examples 1-2,

4-5; see also SEQ ID Nos 3 and 4). It is noted that the instant claims are merely drawn to detection of a "variant gene" (not to, e.g., detection of a predisposition for reduced substrate metabolism in a patient), and to detection of one of three particular polymorphisms. The properties possessed by a particular polymorphism (with regard to whether it increases or decreases the metabolism of any particular substrate) are inherent to it; accordingly, by disclosing detection of the same polymorphism set forth in the claims, the Rebbeck et al reference teaches a "detecting" step that meets the requirements of the claims, and the Rebbeck et al reference anticipates the claims as written. Regarding claim 18, Rebbeck et al disclose determination of whether individuals are homozygous or heterozygous for the cyp3A4 mutation (see, e.g., Example 2). With respect to claim 19, the method disclosed by Rebbeck et al employs genomic DNA and thereby constitutes a type of "genomic DNA assay" (see, e.g., Examples 1, 4-5). Regarding claim 21, Rebbeck et al disclose detection by amplifying a "selected region" of cyp3A4 (see, e.g., Example 2). Regarding claim 24, it is again noted that the manner in which a polymorphism affects metabolism of various substrates is inherent to the polymorphism.

14. Claims 17-21 and 24 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Van Schaik et al (Clinical Chemistry 46(11):1834-1836 [2000]).

It is again noted that the specification discloses at, e.g., page 13, that the CYP3A4 A to G polymorphism disclosed in the specification may be described as being at position –392 of CYP3A4 relative to the CYP3A4 start codon, or at position –290 of CYP3A4 with respect to the CYP3A4 transcription initiation site.

Van Schaik et al disclose and exemplify obtaining DNA samples including the cyp3A4 gene from healthy subjects, and detecting the presence or absence in said samples of the cyp3A4 A to G polymorphism located at position –392 relative to the cyp3A4 start codon (see entire reference, particularly page 1835). It is noted that the instant claims are merely drawn to detection of a "variant gene" (not to, e.g., detection of a predisposition for reduced substrate metabolism in a patient), and to detection of one of three particular polymorphisms. The properties possessed by a particular polymorphism (with regard to whether it increases or decreases the metabolism of any particular substrate) are inherent to it; accordingly, by disclosing detection of the same polymorphism set forth in the claims, the Van Schaik et al reference teaches a "detecting" step that meets the requirements of the claims, and the Van Schaik et al reference anticipates the claims as written. Regarding claim 18, Van Schaik et al disclose determination of whether individuals are homozygous or heterozygous for the cyp3A4 mutation (see, e.g., Figure 1). With respect to claim 19, the method disclosed by Van Schaik et al employs genomic DNA and thereby constitutes a type of "genomic DNA assay" (see, e.g., page 1835, left column). Regarding claim 20, the method of Van Schaik et al comprises a step of digesting amplification products with a restriction enzyme that distinguishes the wild-type and polymorphic versions of cyp3A4 (see, e.g., page 1835). Regarding claim 21, Van Schaik et al disclose detection by amplifying a "selected region" of cyp3A4 (see page 1835). Regarding claim 24, it is again noted that the manner in which a polymorphism affects metabolism of various substrates is inherent to the polymorphism.

15. Claims 17-19 and 24 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Petros et al (Proceedings of the American Association for Cancer Research Annual Meeting 42:266 [3/2001]).

Petros et al disclose obtaining DNA samples including the GSTM1 gene from peripheral blood lymphocytes of patients treated with BCNU, cisplatin, and cyclophosphamide, and detecting the presence or absence in each sample of the GSTM1 null mutation (see entire abstract). It is noted that Petros et al further disclose that patients "homozygous for the GSTM1 null mutation had lower blood concentrations of BCNU," thereby suggesting that, at least with regard to BCNU, the GSTM1 null mutation may be associated with increased (rather than reduced) substrate metabolism. However, the instant claims are merely drawn to detection of a "variant gene" (not to, e.g., detection of a predisposition for reduced substrate metabolism in a patient), and to detection of one of three particular polymorphisms. The properties possessed by a particular polymorphism (with regard to whether it increases or decreases the metabolism of any particular substrate) are inherent to it; accordingly, by disclosing detection of the same polymorphism set forth in the claims, the Petros et al reference teaches a "detecting" step that meets the requirements of the claims, and the Petros et al reference anticipates the claims as written. Regarding claim 18, Petros et al disclose determination of whether individuals were homozygous or heterozygous for the GSTM1 null mutation. With respect to claim 19, the method disclosed by Petros et al employs DNA from peripheral blood lymphocytes, and thereby constitutes a type of "genomic DNA assay." Regarding claim 24, it is again noted that the manner in which the GSTM1

null mutation affects metabolism of various substrates is inherent to the mutation. It is further noted that Applicant's own data indicates increased (rather than decreased) metabolism of BCNU in patients homozygous for GSTM1 null (see, e.g., pages 36 of the specification).

16. Claims 17-19, 21 and 24 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Ambrosone et al (Cancer Research 61:7130-7135 [10/2001]).

Ambrosone et al disclose obtaining DNA samples including the GSTM1 gene from tissues of patients, including patients treated with cyclophosphamide, adriamycin, and 5-fluorouracil, and detecting the presence or absence in each sample of the GSTM1 null mutation (see entire reference, particularly page 7130, right column; page 7131). It is noted that Ambrosone et al disclose that the GSTM1 null genotype was found to be associated with improved overall survival (see entire reference, particularly page 7132). It is also noted that the instant claims are merely drawn to detection of a "variant gene" (not to, e.g., detection of a predisposition for reduced substrate metabolism in a patient), and to detection of one of three particular polymorphisms. The properties possessed by a particular polymorphism (with regard to whether it increases or decreases the metabolism of any particular substrate) are inherent to it; accordingly, by disclosing detection of the same polymorphism set forth in the claims, the Ambrosone et al reference teaches a "detecting" step that meets the requirements of the claims, and the Ambrosone et al reference anticipates the claims as written. Regarding claim 18, Ambrosone et al disclose determination of whether individuals were homozygous for the GSTM1 null mutation (see, e.g., page 7130, right column).

With respect to claim 19, the method disclosed by Ambrosone et al employs DNA from tissue samples, and thereby constitutes a type of "genomic DNA assay." Regarding claim 21, Ambrosone et al disclose detection by amplifying a "selected region" of GSTM1 (see page 7130, right column). Regarding claim 24, it is again noted that the manner in which the GSTM1 null mutation affects metabolism of various substrates is inherent to the mutation.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Petros et al (Proceedings of the American Association for Cancer Research Annual Meeting

42:266 [3/2001]) in view of Ambrosone et al (Cancer Research 61:7130-7135 [10/2001]).

Petros et al disclose obtaining DNA samples including the GSTM1 gene from peripheral blood lymphocytes of patients treated with BCNU, cisplatin, and cyclophosphamide, and detecting the presence or absence in each sample of the GSTM1 null mutation (see entire abstract). It is noted that Petros et al further disclose that patients "homozygous for the GSTM1 null mutation had lower blood concentrations of BCNU," thereby suggesting that, at least with regard to BCNU, the GSTM1 null mutation may be associated with increased (rather than reduced) substrate metabolism. However, the instant claim is merely drawn to detection of a "variant gene" (not to, e.g., detection of a predisposition for reduced substrate metabolism in a patient), and to detection of one of three particular polymorphisms. The properties possessed by a particular polymorphism (with regard to whether it increases or decreases the metabolism of any particular substrate) are inherent to it; accordingly, by disclosing detection of the same polymorphism set forth in the claims, the Petros et al reference teaches a "detecting" step that meets the requirements of the claims, with the exception of not teaching "amplifying a selected region" of the gene in order to accomplish detection, as required by claim 21. Ambrosone et al disclose that the GSTM1 null mutation may be rapidly detected in a multiplex PCR amplification that also detects other mutations associated with variations in the metabolism of chemotherapeutic agents (see entire reference, particularly page 7130). It is a property of the GSTM1 PCR employed by Ambrosone et al that it amplifies a region of GSTM1 that was

"selected" by Ambrosone et al. In view of the teachings of Ambrosone et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Petros et al so as to have employed the PCR method taught by Ambrosone et al in determining GSTM1 genotype. As Petros et al do not reveal the method used to achieve genotyping, an ordinary artisan would have been motivated to have used the method of Ambrosone et al – rather than to have experimented to identify a particular method for use in GSTM1 genotyping – for the advantages of convenience and efficiency. Further, as Ambrosone et al disclose conditions that may be used successfully both to genotype GSTM1 and another gene associated with variations in cancer survival and success of cancer treatments, an ordinary artisan would have been motivated to have made such a modification in order to have rapidly determined a patient's genotype for multiple genes simultaneously, thereby facilitating more rapid diagnosis and treatment.

Conclusion

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
October 6, 2003